Detection of Chronic Respiratory Bronchiolitis in Oxidant-Exposed Populations: Analogy to Tobacco Smoke Exposure

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Studies in nonhuman primates indicate that one pathophysiologic consequence of ozone exposure is chronic bronchiolitis in terminal bronchioles. Modeling dosimetry suggests that a similar phenomenon is possible in humans. These findings may constitute an important analogy to the respiratory bronchiolitis that is associated with tobacco smoking in young adults. This analogy could form the basis for future research related to chronic respiratory health effects of ozone. The smoking data are reviewed and several research strategies are proposed that will be developed more fully in subsequent articles in this volume. — Environ Health Perspect 101(Suppl 4):217–218 (1993).

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Laboratory studies in animals and controlled exposure studies in humans consistently have demonstrated an upper and lower respiratory tract inflammatory response to ozone exposure. The hallmark of this response is the polymorphonuclear leukocyte, but other markers of activated inflammatory and repair responses have been observed. These phenomena probably are accompanied by increased lung permeability. Animal studies of the effect of ozone exposure, including most particularly those on nonhuman primates (*1*), suggest that one pathophysiologic consequence of the inflammatory response to prolonged or repetitive ozone exposure is a chronic bronchiolitis in terminal bronchioles. This is consistent with modeling dosimetry calculations that indicate that this zone will be the location of maximal deposition in the human (*2*). The animal database has shown that primates are more sensitive to ozone exposure than rodents and that morphological changes induced with long-term or repetitive exposures are not reversible.

A report by Sherwin and Richters (*3*) of studies of the autopsy lungs of 107 youths between 14 and 25 years who died of nonrespiratory causes in Los Angeles indicates that a severe chronic bronchiolitis was present in the same region of the lung in one-third of the cases. Although quantitative morphometry on the specimens and control data from other, less polluted cities are not yet available, these preliminary observations offer impetus to the search for a relationship between respiratory bronchiolitis and ozone exposure.

The above observations suggest that there may be an important analogy to the respiratory bronchiolitis associated with tobacco smoking in young adults (*4*). Studies of the respiratory bronchiolitis that has been associated with cigarette smoking are reviewed briefly to illustrate the types and limitations of data that will be required to establish a similar link in relationship to chronic ozone exposure.

Respiratory bronchiolitis of variable sever-ity in smokers was first described by Niewohner and his colleagues (*4*). A recent comparison of small airway inflammation in 42 smokers and 13 nonsmokers in Vermont (*5*), in which the bronchiolar changes were evaluated by quantitative morphometry, indicated that in the 20- to 30-year-old subjects, the mean score for bronchiolar wall inflammation was about three times larger in smokers than nonsmokers. This confirms earlier work indicating the same phenomenon.

The physiological correlates [tests of small airway function) of these changes have been noted in many surveys (more than 70 in 1989 (*6,7*)] of smokers and nonsmokers. These findings can be summarized as tests of small airway function that indicate differences between smokers and nonsmokers (even in teenagers) in the following parameters (*1*): *a*) single breath nitrogen slope, *b*) closing volume, *c*) mid-expiratory flow rates, *d*) change of dynamic compliance with respiratory frequency, *e*) differences in regional ventilation in the lung measured with radioactive xenon, and *f*) changes in alveolar-arterial oxygen tension differences with posture. Of particular importance is the fact that all of these differences have been documented to occur when the FEV_1 is still normal or nearly so (95% of predicted).

Because it is not clear yet whether cigarette smoking induces a premature loss of lung recoil (*6*), the elevation of residual volume (that could produce the above pathophysiologic changes) found in 30-year-old smokers before FEV_1 has been reduced might be due to loss of recoil and/or to the small airway lesions noted above. It has been reported that in smokers small airway tests are not predictive of later FEV_1 decline (*8*). However, the observation that smoking cessation is followed by small, but significant, functional improvement (*9,10*) supports the view that reversible respiratory bronchiolitis may be present.

Given the acute inflammatory responses that have been observed with ozone exposure, the recent study by Richards et al. (*11*) provides an important bridge between the smoking data and possible effects of ozone exposure. These investigators observed that the fall in midexpiratory flow rates in smokers under the age of 30 was accompanied by increasing levels of neutrophil activation (measured by chemiluminescence). In 60 healthy young smokers (mean age 28 years), the flow rate tests of small airway function were performed in a laboratory setting. The standard error of the mean of the tests varied between 1.1 and 4.9. The mean FEF25-75, as a percent

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of predicted, was 121.9% in the group with the least affected function and 71.3% in the worst group. The mean FEV1 was 105.5% of predicted in the former and 94.9% of predicted in the latter group. Although the midexpiratory flow rate measurements have a higher coefficient of variation than the FEV_1, it is clear from this study that they not only possess much more discrimination than the FEV_1 in relation to the early changes in smokers (which morphological studies have indicated are changes of bronchiolitis), but they also have a sufficiently low coefficient of variation to be used for this purpose, at least in the laboratory setting.

There is no evidence that the early appearance of respiratory bronchiolitis in smokers is related to the later development of emphysema. Perhaps this is not surprising in view of the known complexity of the steps that lead to lung destruction. For this reason, some physicians have dismissed too readily the considerable body of evidence indicating that smoking induces respiratory bronchiolitis. There is subsequent evidence from studies of occupationally exposed cohorts and individual cases (*6*) that midflow rates predominately reflect small airway changes; this is true in allergic alveolitis, exposures to irritant gases, and dust exposures, including asbestos. Sarcoidosis and postviral bronchiolitis provide the best examples of nonoccupational small airway involvement (*6*).

Two approaches address the question of whether oxidant exposure is associated with respiratory bronchiolitis. The study of Sherwin and Richters (*3*) suggests that the use of autopsied lungs would be of value, and this approach is developed in detail by Lippmann in this volume (*12*).

The study of Richards et al. (*11*) suggests that biological markers of inflammation, in conjunction with the appropriate measures of small airways' functions, would offer another fruitful approach to this problem. Devlin's paper in this volume (*13*) provides details on markers of ozone exposure, and Hatch and Thomas' paper (*14*) provides general guidelines for the utility and application of biological markers in epidemiologic studies. Moreover, the issues of site selection for studies; the requirements for valid, retrospective exposure assessment; and the selection of metrics for ozone exposure are detailed by Lippmann. Studies that employ biological markers of response to ozone in conjunction with appropriate measures of lung function would be important adjuncts to data derived from autopsy studies and studies derived from controlled exposures to ozone (*13,15*) that seek to define more clearly the biochemical and cellular responses of the lung to ozone exposure.

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